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Sexual dysfunctions (SD) and selective serotonin reuptake inhibitors (SSRIs): from preclinical studies to intervention strategies

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ABSTRACT

In the light of existing literature, we reviewed the causes, management and potential therapeutic benefits of SSRI (Selective serotonin reuptake inhibitor) agents regarding sexual functions. (SSRIs) are the most commonly used medications for the treatment of depression, based on their effectiveness and safety profile. Sexual dysfunctions (SD) caused by SSRIs are one of the most important reasons for discontinuation of treatment in both genders. Knowing the intervention strategies in patients who develop SD is pivotal for the proper management of sexual side effects and the treatment adherence of patients. The effects of SSRIs on sexual functions can also be used to treat certain disorders. SSRIs have a high success rate in the treatment of premature ejaculation and their off-label use for this purpose is widely recognized.

Keywords: Selective serotonin reuptake inhibitors, sexual dysfunctions, ejaculation disorders

INTRODUCTION

Selective serotonin reuptake inhibitor (SSRI) drugs have been the most commonly used drugs in the world for the last 30 years for major depression treatment. SSRIs are recommended as first-line therapy for the treatment of moderate to severe depressive disorders.[1] Six widely used SSRI molecules currently available on the market are, fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. Five of these SSRI molecules -other than fluvoxamine- also are indicated for panic disorder, social anxiety disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and premenstrual dysphoric syndrome treatments. Besides their indicated use, above mentioned molecules can also be treatment alternatives for fibromyalgia and premature ejaculation as off-label medication choices.[2]

SSRI group drugs are considered to be relatively safe, due to their low incidences of anticholinergic side effects (excluding paroxetine), particularly when compared to tricyclic antidepressants in terms of cardiac adverse effects, and they have a wide therapeutic index. Due to mentioned advantages, these molecules became increasingly used drugs all over the world. The prevalence of SSRI use in general population has been reported to be 3.5%.[3]

Based on multiple comparative studies, SSRIs and other antidepressants have not been found to be superior to each other in terms of treatment effectiveness. However, SSRIs tuned out to have higher patient compliance because they have more tolerable side effects.[2] Randomized controlled clinical trials showed that, SSRIs have more or less equivalent antidepressant efficacy. On the other hand, there may be individual differences in pharmacokinetics and pharmacodynamic aspects, which may affect clinical responses among patients, therefore some patients may respond better to a particular SSRI than to another.[4]

All SSRIs are ligands of serotonin transporter (SERT) and they basically inhibit serotonin transportation, thereby increase the synaptic availability of serotonin that remains in the synaptic cleft and bind to postsynaptic receptors. This enhanced persistence of serotonin and accordingly increased serotonergic activity in the central nervous system (CNS) however, also lead to a decrease in the number and sensitivity of postsynaptic serotonin receptors (5-HT receptors). Each member of the SSRI family can affect SERT to a different degree. Escitalopram for instance, has the highest known SERT selectivity. SSRIs also differ in terms of different parameters such as elimination half-life and their ability to inhibit cytochrome P450 (CYP) enzymes.[2]

One of the most common clinical side effects associated with SSRI use is sexual dysfunction (SD). The prevalence of

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sexual side effects in patients receiving SSRI therapy is found as high as 50-70% in various studies. Common symptoms include decreased libido, difficulty in raising the arousal, and delayed or failure of orgasm.[5-7] In fact, the incidence of SD seems to be higher than the number of SDs being reported. In a study, only 14% of patients who experienced SD due to antidepressant use spontaneously reported this side effect to their physician.[8] The development of SD is an important issue since it leads to the discontinuation of the treatment[9] and has been shown to lead to poor adherence patterns in patients who choose to continue SSRI therapy.[10]

Serotonin is a neurotransmitter that is effective in all three phases of sexuality: desire, arousal and orgasm. The increase in serotonin levels that develops with SSRI use seems to play a role in the development of SD by inhibiting libido, ejaculation and orgasm. Main SD associated with SSRI use are lack of desire, loss of arousal as erectile dysfunction, delayed orgasm or anorgasmia, and delayed ejaculation. Although the underlying mechanisms regarding the causes of SDs due to SSRI use remain partially understood, the distribution and the interaction of serotonin with various other neurotransmitters, may help explain some features of the adverse actions of these agents. The effect on lack of desire may be related to serotonin induced reduction in dopamine levels in the CNS. Additionally, SSRIs may inhibit nitric oxide synthase, leading to impaired erectile function.[11]

This review focuses on SD due to SSRI use, especially ejaculation problems, which are amongst the most common SD types seen in male patients. Clinical and preclinical studies investigating the ejaculation problems due to SSRI use were reviewed in the light of current literature and therapeutic approaches were summarized.

SD DUE TO SSRIS

Treatment response to SSRIs may differ between men and women. Various studies have shown that women may respond better to SSRIs than men.[12] SD and other side effects associated with SSRIs may also differ based on gender. These differences may be due to gender-related variations in the pharmacokinetic profile.[12-13] Genetic differences in liver cytochrome enzyme systems may cause individual differences in side effects of SSRIs. Genetically poor metabolizers are expected to have higher blood SSRI concentrations and therefore potentially have a greater risk of side effects compared to ultra-rapid metabolizers.[14]

SSRIs can cause SD both in men and women. SDs can occur either in a single phase of sexuality -lack of desire, loss of arousal, orgasmic dysfunctions- or can be seen in multiple phases. The main sexual side effects observed in women using SSRIs are decreased sexual desire, decreased vaginal lubrication, and anorgasmia. The main sexual side effects observed in men using SSRIs are decreased sexual desire, delayed ejaculation or anorgasmia, and erectile dysfunction.[15]

Although SD appears to be a side effect of all antidepressants at different rates (such as tricyclic antidepressants, MAO enzyme inhibitors, venlafaxine, duloxetine, etc.), the highest prevalence has been reported for SSRI drugs. In a meta-analysis, the incidence of SD after SSRI use was found to be 27.4% with sertraline, 20% with citalopram, 16.6% with paroxetine, and 15.5% with fluoxetine.[16] According to post-hoc analyzes of data from the multicenter STAR-D (Sequenced Treatment Alternatives to Relieve Depression) study, in which over 4000 patients with depression were followed-up, SD incidence was found 21% in patients whose depressions were in remission with citalopram treatment.[17]

Despite SD is a very common adverse effect of SSRI use, it is a subject that patients may have difficulty in expressing their problem, unless specifically questioned by a physician or a therapist, thus the frequency of SD developing with SSRI use cannot be determined exactly. It has been found that female patients using antidepressants are less likely to report developing SD to their physicians than male patients.[18]

Various studies were aimed to find out which phases of sexuality are most affected by SSRI use in men and women. In a study evaluating the sexual side effects of SSRIs, paroxetine was found to be associated with a greater incidence of sexual side effects than other SSRIs. Analysis of phase-specific sexual function showed that anorgasmia, erectile dysfunction, and decreased vaginal lubrication were more associated with paroxetine.[8]

In a study comparing SD developing in 1022 patients using SSRIs, the highest rate of development of SD was found to be associated with citalopram (72.7%) and paroxetine (70.7%). The development of SD due to sertraline, fluvoxamine and fluoxetine was found to be 62.9%, 62.3% and 57.7%, respectively.[17] Another study of patients taking fluoxetine, paroxetine, and sertraline found that all three drugs reduced libido (55%), arousal (50%), duration of orgasm (36%), and intensity of orgasm (42%) equally during treatment.[19] Ekselius et al.[5] compared the effects of sertraline and escitalopram on SD, where no significant difference was found in the prevalence rates of phase-specific SD. Clayton et al.[20] reported that men are more likely to experience dysfunction in the desire and orgasm phase and less likely to experience dysfunction in the arousal phase compared to women.

Since SD due to SSRI use is one of the most important reasons for discontinuation of anti-depressant therapy[17]; clinicians should be careful about this adverse effect and monitor their patients. In some of the patients SD improves over time, whereas some patients with SD complaints, do not exhibit an improvement during the treatment course, and in some patients complaints may even worsen over time.[21] The signs of SD development during depression therapy are important for the clinician to recognize, as it not only causes the patient to discontinue the treatment, but also causes decreased self-esteem problems in relationship with their partners and a reduction in their quality of life.[21]

Although SD due to SSRI use is an important therapy problem, this effect can be used for the treatment of particular diseases. In the treatment of conditions such as paraphilia, the libido-reducing side-effects of SSRIs are utilized.[22] One of the important occasions where SSRIs are used off-label in clinical practice, is premature ejaculation (PE). SSRIs

delaying effect on ejaculation time is used for the treatment of patients diagnosed with PE.

PREMATURE EJACULATION AND USE OF SSRIS IN PE TREATMENT

Ejaculation consists of two major physiological phases, emission and expulsion. Ejaculation is completed with the expulsion of semen from the urethra. In the emission phase, rhythmic contractions occur in the epididymis and vas deferens, under the stimulation of sympathetic fibers originating from the medulla spinalis. This rhythmic movement forces seminal fluid to pass into the urethra. Later, in the ejection phase, which is mainly controlled by sacral parasympathetic fibers, semen is expelled from the urethra by the relaxation of external urethral sphincter and rhythmic contractions of the bulbospongiosus and bulbocavernosus muscles.[23] Any problem occurring in one of these two phases may cause dysfunctions such as premature ejaculation, late ejaculation, retrograde ejaculation, and failure to ejaculate.

The most common disorder among male SD is premature ejaculation (PE). There are study results reporting the frequency of PE as 20-30%.[24,25] The diagnosis of PE is a self-reported diagnosis, and different authorities have established different diagnostic criteria for PE. One of the most commonly used diagnostic criteria was determined by the International Society of Sexual Medicine (ISSM). To diagnose PE according to ISSM criteria, from the first sexual intercourse onwards, ejaculation must always and almost always occur before or within approximately one minute after vaginal penetration.[26]

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), published in 2013, PE was defined as a man's ejaculation within 1 minute and a feeling of lack of control during ejaculation. The symptoms must last longer than six months and are not due to another mental disorder (DSM-5).[27]

With the introduction of SSRI drugs in the treatment of PE, significant success has been achieved.[28] Numerous previous clinical studies have shown that the use of SSRIs prolongs the ejaculation time.[29]

The effects of a SSRI during acute and chronic use differ significantly at the molecular level. After acute administration of an SSRI, existing SERTs are blocked, which increases the level of serotonin in the synaptic cleft. Increased serotonin levels activate 5-HT1A and 5-HT1B auto-receptors, and as a result, less serotonin is released into the synaptic cleft within minutes. Under physiological conditions, the net effect of acute SSRI administration is only a slight or no increase in 5-HT neurotransmission. With extended use of SSRIs, a progressively increasing level of serotonin is seen in the synaptic cleft due to long-term blockade of SERT. Over time, desensitized 5HT1A receptors become unable to suppress serotonin release from the presynaptic cell. Thus, with chronic use of SSRIs, the level of serotonin in the synapse increases significantly. The duration of chronic administration (average 2-3 weeks) is the time during which the clinical antidepressant effect of SSRIs begins. The inhibitory effect of SSRIs on ejaculatory behavior is more pronounced when administered chronically than when administered acutely.[30]

Despite the late onset of their antidepressant effects, SSRIs appear to be effective in preventing premature ejaculation after both acute and chronic administrations.[31] The mechanism by which their effects on premature ejaculation occur within hours, is not fully understood. It is thought that acute administration delays ejaculation through a direct inhibitory action of increased serotonin on ejaculation.[31]

Previous preclinical and clinical studies have consistently shown that decreased serotonin neurotransmission, 5-HT2C receptor hyposensitivity, and 5-HT1A receptor hypersensitivity may play a role in the physiology of premature ejaculation.[32]

Off-label use of SSRIs, particularly paroxetine, sertraline fluoxetine, and citalopram, is a first-line pharmacotherapy intervention in the treatment of premature ejaculation.[33] Paroxetine appears to be the most studied SSRI in the literature, and reviews examining the use of paroxetine in the treatment of premature ejaculation have shown its effectiveness in premature ejaculation management.[31]

A meta-analysis of 19 randomized controlled trials examining the effectiveness of SSRIs in the treatment of premature ejaculation found fluoxetine, escitalopram, and paroxetine to be effective in treatment, with paroxetine having a higher treatment success than other agents.[34] On the other hand, there are also study results that show no significant difference between SSRIs.[35]

Dapoxetine, a specific SSRI manufactured solely for the treatment of premature ejaculation, is also used in the treatment. Dapoxetine is an SSRI with a short half-life of 19 hours that is approved for the treatment of PE in many countries. Dapoxetine is administered in doses of 30 mg and 60 mg, 1 to 3 hours prior to the intercourse and has been shown to significantly prolong the time to ejaculation.[36,37]

There are currently various options for PE treatment other than SSRIs and Dapoxetine. Treatment can be provided with special sexual therapy techniques using developed behavioral techniques.[33] Phosphodiesterase type 5 inhibitors (i.e. sildenafil) are used in the treatment of PE cases accompanied by erectile dysfunction.[38] Although topical local anesthetics such as lidocaine were widely used in the past to reduce the sensitivity of the glans penis and delay ejaculation, they are no longer preferred. Tramadol, a centrally acting opioid analgesic, prolongs the ejaculation period by inhibiting the reuptake of serotonin and norepinephrine. However, it is not a frequently used agent due to the development of tolerance to tramadol, its potential for dependence, and the risk of respiratory depression at high doses.[39]

Clinical studies alone are insufficient to explain the mechanism by which SSRIs prolong ejaculation time. The effects of SSRIs on ejaculation physiology have also been studied in many preclinical studies.

EFFECTS OF SSRIS ON EJACULATION PHYSIOLOGY: DATA FROM PRECLINICAL STUDIES

The control of ejaculation in the CNS, medulla spinalis and genital tract is regulated in a complex manner by many neurotransmitters and neuromodulators, including

serotonin, dopamine, noradrenaline, oxytocin, nitric oxide (NO) and ATP.[28] Serotonin and the serotonergic system are important in the regulation of ejaculation, both in the central and peripheral nervous systems. The available evidence to date suggests that the general effect of serotonin on ejaculation is inhibitory.[40]

In the nervous system, serotonergic activity is controlled by presynaptically located 5HT1A and 5HT1B auto-receptors and the SERT. When serotonin is released from axonal terminals, it binds to serotonin receptors and causes a wide range of effects. Under normal conditions, serotonin is transported from the extracellular space back to the presynaptic neuron via SERT, thereby terminating its effect. SSRI group drugs block the reuptake of serotonin from the synaptic cleft by inhibiting SERT, thus increasing the serotonin concentration.[41] The function of 5HT1A and 5HT1B auto-receptors is to prevent serotonergic hyperstimulation, by suppressing the release of serotonin.[41]

Systemic administration of SSRIs has been shown to increase serotonin levels in the rat brain by 2 to 4-fold within one hour.[42] Microinjection of serotonin into the serotonergic projection area in the forebrain has been reported to prolong ejaculation latency in rats.[43]

Sympathetic nerves originating from the thoracolumbar region of the spinal cord and parasympathetic nerves originating from the sacral region integrate peripheral and central signals, ensuring that ejaculation occurs normally. There is an intense serotonergic transmission from the CNS to the spinal cord. 5-HT1A, 5-HT1B and 5-HT2C receptors are intensely expressed in the sacral parasympathetic nucleus of the spinal cord.[43]

Ejaculation latency was shortened in rats after systemic administration of 8-OH-DPAT, a selective agonist of 5-HT1A receptors. Consistent with the effect of serotonin to inhibit ejaculation, 8-OH-DPAT blocks this inhibitory effect by reducing the release of serotonin into the synaptic cleft.[44] Subcutaneous administration of 5-HT1B receptor agonists (anpyrtoline, TFMPP), whose expression is shown in the hypothalamus and at the lumbosacral level of the spinal cord, has been shown to impair ejaculation in rats.[45] Systemic acute administration of 5-HT2C agonist DOI has been shown to suppress ejaculation in rats, and ejaculation is restored by the administration of 5-HT2C antagonists.[46]

Preclinical findings support clinical study results. It has been found that activation of 5-HT1A receptor accelerates ejaculation, while activation of 5-HT1B and 5-HT2C receptors plays an inhibitory role in ejaculation.[47] Recent studies have repeatedly demonstrated the important role of serotonin 5-HT2C receptors in the regulation of ejaculation. 5-HT2C antagonist drugs, such as lorcaserin, have been shown to shorten the time to ejaculation.[48]

Current preclinical data demonstrate that 5-HT1A receptors play an important role in ejaculation control. Based on these study results, researchers have sought to develop selective antagonists that directly target 5-HT1A auto-receptors, suggesting that this could provide specific treatment for PE. Some researchers found that specific 5-HT1A receptor blockade did not affect ejaculation time.[47] However, administration of a 5-HT1A antagonist with an SSRI resulted in a significant prolongation of ejaculation latency.[49] This finding also supports that 5-HT1A receptors are activated only when serotonin levels are elevated (auto-receptor activity).

Although some studies have shown acute inhibition of ejaculation by administration of molecules such as paroxetine and fluoxetine,[28,50] it has been shown that long-term treatment with paroxetine and fluoxetine is more successful in delaying ejaculation.[51] The delayed onset of ejaculation due to SSRI agents is similar to the late onset of antidepressant activity of SSRIs and suggests that desensitization of 5-HT1a auto-receptors is required for delayed ejaculation.[41] 5-HT1a receptors may co-localize with 5-HT7 receptors in the cell membrane,[52] and it has been hypothesized that hetero-dimerization of these receptors may facilitate the desensitization of 5-HT1A auto-receptors induced by SSRIs.[53]

Ejaculation delaying effects of SSRIs seems to be determined not only at the level of serotonin and serotonin receptors but also by some genetic variations. Some research results with SERT knockout rats provide important evidence in this context. Male SERT knockout rats (SERT– / –) exhibit a strong genotype with lower basal ejaculation performance compared to carrier (SERT+/+) or heterozygous serotonin carrier rats (SERT+ / –).[54] Results from another study found that, (SERT–/–) rats had up to a nine-fold increase in extracellular serotonin levels,[55] a decrease in the number of ejaculations, and an increase in ejaculation latency compared to (SERT+/+) rats.[56] It has been shown that differences in SERT genetic variants may be responsible not only for the sexual side effects but also for other adverse effects of SSRI drugs (nonspecific adverse effects such as nausea, vomiting, dizziness, etc.).[57]

INTERVENTION STRATEGIES FOR SSRI-RELATED SD

While nonspecific side effects such as gastrointestinal intolerance (nausea, loss of appetite, vomiting, diarrhea) that frequently develop due to SSRIs often improve with continued use of the drug,[58] sexual side effects have been reported to persist in up to 80% of cases.[59]

In a meta-analysis of 62 randomized controlled trials involving over 6000 patients examining the development of sexual side effects related to antidepressant use, it was shown that sexual side effects related to SSRI and tricyclic antidepressants were one of the most important reasons for discontinuation of treatment. It has been understood that 14% of patients using SSRIs discontinued their treatment due to sexual side effects related to SSRIs.[60]

Researchers have found that, if left untreated, SD can have even more negative effects on the quality of life that is already poor due to depression, can affect interpersonal relationships, and can negatively impact the patient's self-esteem.[61]

In a patient who develops SD due to SSRI, the recommended options to control the undesirable side effects are as follows: waiting for SD to resolve spontaneously, reducing the dose of

SSRI used, changing the medication, trying to reduce the side effects with a drug holiday or add-on treatment.[62]

Figure 1 summarizes the intervention strategies that clinicians can use in the management of SD due to SSRI use.

Figure 1. Management of sexual dysfunctions due to selective serotonin reuptake inhibitor use

WAITING FOR SPONTANEOUS IMPROVEMENT

In two studies on waiting for spontaneous improvement without changing the drug in SSRI-induced SD, partial recovery rates are reported in the range of 14% to 20% and complete recovery rates between 6% and 10% at a 6 month time period.[17,63] The rate of spontaneous improvement of side effects by this approach seems to be quite low. In fact, this situation may be preferred because it does not require additional medication or intervention; however, patient selection is very important. For patients whose treatment is likely to end within a few months at the latest, it may be preferable to wait for spontaneous improvement. In addition, in patients with mild to moderate sexual side effects who do not experience any significant distress from these side effects, waiting may be preferred. The decision to wait should be made together with the patient.

REDUCING THE DOSE OF SSRI

If the patient is being treated with high doses of SSRIs, reducing the dose of SSRIs may be considered as an option to reduce sexual side effects. Current data suggest that SSRI-associated side effects are related to the SSRI dose. Therefore, reducing the SSRI dose may be helpful in relieving side effects.[64] One study found that reducing the current medication dose by 50% -in patients with SD due to SSRI treatment- provided significant improvement in sexual functions.

However, this strategy cannot be used in every patient, as some patients may experience sexual side effects even at starting doses.

When reducing the dose to improve side effects, care should be taken not to get below lower than minimally required dosage, which will provide the minimum effective concentration. It should be noted that sub-therapeutic doses of medication will reduce the severity of sexual side effects but may also cause relapse of depression. Reducing the dose of medication is a method that can be preferred during maintenance therapy, but only when the acute phase of the disease has regressed and the symptoms are under control. Reducing the dose is not preferred in patients whose depressive symptoms are not yet under control, as it may increase the risk of relapse. When reducing the dose of an SSRI, rapid reduction is not preferred. The dose should be reduced gradually and carefully. If the patient adapts to gradual dose reduction, then this approach should be preferred.

Drug Holiday

Drug holidays can be defined as temporarily reducing the dose of a drug or pausing for a short period of time (a few days, in general). Drug holiday is a method that can only be used if sexual activity is scheduled.

For an SSRI with a short half-life, such as paroxetine, a drug holiday may involve postponing the time of taking the drug until after sexual intercourse. To date, only one clinical trial has been conducted to evaluate the effect of drug holidays on SSRI-induced SD. This study reported that drug holidays improved sexual function in sertraline and paroxetine users. However, there was no improvement in sexual side effects in those taking fluoxetine. The authors speculated that this may be due to the long half-life of fluoxetine.[65] In a recently published randomized controlled trial, patients who developed SD due to SSRI use were given a drug holiday twice a week, and at the end of 8 weeks, a significant difference was observed between the control group and the intervention group in terms of side effects. It has been determined that sexual side effects that developed in patients who took a drug holiday improved and that there was no worsening of existing mental illness with the drug holiday.[66]

A long drug holiday carries the risk of causing symptoms to relapse. Alternative approaches include using a lower dose (approximately half) of the drug during periods of expected or planned sexual activity. It is not appropriate to use the drug holiday method in patients using SSRIs with long half-lives such as fluoxetine.

Switching Medication

It may involve changing the current SSRI molecule to a drug from a different group known to have fewer sexual side effects, such as selective serotonin noradrenaline reuptake inhibitors (SNRIs), vortioxetine, agomelatine, and monoamine oxidase inhibitors.[67] If sexual side effects are severe, and cause great distress to the patient, or if there are other side effects of the drug other than sexual side effects, and if the expected treatment response is not achieved with the current drug, a change in antidepressant medication is recommended.[67] If the patient is not benefiting from the SSRI treatment he or she is using, changing the antidepressant would be a logical attempt. Current literature suggest that SSRIs and SNRIs cause more SD compared to placebo, however agomelatine, bupropion, moclobemide, nefazodone and mirtazapine have been found to have very low SD side effects.[68] As explained in the previous section; since SSRIs do not differ significantly from each other in terms of the risk of developing sexual side effects, switching from one SSRI to another is not recommended.

Several randomized controlled trials have found that, exchanging SSRI therapy with bupropion, improves sexual side effects.[15] There are also study results showing that there is a significant improvement in sexual side effects when SSRI treatment is replaced with mirtazapine.[69] Another study, changing from an SSRI to nefazodone, reported an improvement in sexual function.[70]

There are also study results showing significant improvement in sexual side effects with switching from SSRI to vortioxetine[71] and agomelatine.[72]

Switching Medication

Another intervention strategy in patients with drug-induced SD is to add a molecule that has been shown to reduce sexual side effects to the SSRI treatment. Add-on therapy is generally applied to patients who have seen significant benefits from their current SSRI treatment and who do not want to change their medication. Add-on treatment is most commonly done by adding an antidepressant from a different group (i.e. bupropion, mirtazapine, trazodone), adding a phosphodiesterase-5 inhibitor (sildenafil, tadalafil), or adding a 5-HT1A partial agonist (buspirone) to the existing SSRI regimen.

Patients who have benefited from their SSRI treatment, who do not plan to change their treatment, and who are expected to continue antidepressant treatment for a longer period of time are suitable patients for add-on treatment.[68]

Among add-on strategies, bupropion might have the most strong evidence for efficacy and tolerability.[73] A cochrane meta-analysis reported that adding 300 mg of bupropion to SSRI therapy significantly reduced sexual side effects.[74] Results of another randomized controlled trial in which 150 mg/day bupropion was added to SSRI treatment showed that adding bupropion to the treatment produced a similar enhancement.[75,76]

The addition of phosphodiesterase-5 inhibitors to SSRI treatment has been tried most frequently in male patients who developed erectile dysfunction due to SSRIs. Randomized controlled trials have shown that adding 50 mg sildenafil to SSRI treatment reduces drug-induced erectile dysfunction.[77,78]

In one study, sildenafil was added to men and women using SSRIs, and it was shown that SD symptoms such as decreased libido and decreased arousal were reduced in both men and women.[79]

Addition of 30 mg/day mirtazapine to SSRI treatment has also been shown to reduce sexual side effects.[80]

In two randomized controlled trials evaluating the addition of the 5-HT1A partial agonist buspirone to SSRI treatment, was found to reduce the incidences of SDs,[81,82] whereas the addition of cyproheptadine, a 5HT2C receptor antagonist, and ginkgo biloba to the treatment did not significantly improve sexual side effects.[68]

In summary, the decision on which of the five suggested intervention strategies presented above to choose should be made on a completely patient-specific basis. The appropriate strategy should be selected by taking into consideration many factors, such as the degree of distress caused by sexual side effects, the presence of drug-related other side effects, the duration of treatment, and the patient's comorbid diseases. The patient should be informed about possible intervention strategies and included in the decision-making process. This aims to increase the patient's compliance with treatment. In questioning and monitoring SD due to SSRI use in patients, it is recommended to use scales that evaluate sexual function in detail such as international erectile dysfunction index and sexual function questionnaire.[68]

CONCLUSION

In conclusion, due to their effectiveness, safety and cost-effectiveness, SSRI drugs are among the most important and first choice drugs in the treatment of many psychiatric diseases, especially depression. As summarized above, current literature indicates that SSRI-induced SD is quite often. Since waiting for a recovery without amending drug regimen can negatively impact treatment compliance, it is crucial to address SD side effects proactively. The recommended options to control the undesirable side effects are waiting for SD to resolve spontaneously, reducing the dose of SSRI used, changing the medication, trying to reduce the side effects with a drug holiday or add-on treatment. Each intervention strategy should be tailored individually to the patient, considering the benefit they derive from their current treatment, the degree of remission, and any coexisting medical conditions.

Finally, current information in the literatue highlight the importance of actively inquiring about possible sexual side effects in order to detect probablre SDs. Understanding the molecular basis of sexual side effects caused by SSRIs is also highly important for the development of new drugs and treatment strategies in this area.

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The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). *Am J Psychiatry.* 2000;157(Suppl):1-45.
2. Edinoff AN, Akuly HA, Hanna TA, et al. Selective serotonin reuptake inhibitors and adverse effects: a narrative review. *Neurol Int.* 2021;13:387-401.
3. Olie´JP, ElomariF, Spadone C, Le´pine JP. Antidepressants consumption in the global population in France. *L' Encephale.* 2002; 28:411-417.
4. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. Güneş Tıp Kitabevi, Ankara. 2022;2:3155-3160.
5. Ekselius L, von Knorring L. Effect on sexual function of long-term treatment with selective serotonin reuptake inhibitors in depressed patients treated in primary care. *J Clin Psychopharmacol.* 2001;21(2):154-160.
6. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. *J Affect Disord* 2002; 68:167-181.

7. Fava M, Rankin M. Sexual functioning and SSRIs. *J Clin Psychiatry.* 2002; 63(Suppl 5):13-16.
8. Montejo-González AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther.* 1997;23:176-194.
9. van Geffen EC, van der Wal SW, van Hulten R, de Groot MC, Egberts AC, Heerdink ER. Evaluation of patients' experiences with antidepressants reported by means of a medicine reporting system. *Eur J Clin Pharmacol*. 2007; 63(12):1193-1199.
10. Perlis RH, Laje G, Smoller JW, Fava M, Rush AJ, McMahon FJ. Genetic and clinical predictors of sexual dysfunction in citalopram-treated depressed patients. *Neuropsychopharmacology.* 2009;34:1819-1828.
11. Keltner NL, McAfee KM, Taylor CL. Mechanisms and treatments of SSRI-induced sexual dysfunction. *Perspect Psychiatr Care*. 2002; 38:111-116.
12. Sramek JJ, Murphy MF, Cutler NR. Sex differences in the psychopharmacological treatment of depression. *Dialogues Clin Neurosci*. 2016;18:447-457.
13. Sramek JJ, Cutler NR. The impact of gender on antidepressants. *Curr Top Behav Neurosci*. 2011;8:231-249.
14. Shalimova A, Babasieva V, Chubarev VN, Tarasov VV, Schiöth HB, Mwinyi J. Therapy response prediction in major depressive disorder: current and novel genomic markers influencing pharmacokinetics and pharmacodynamics. *Pharmacogenomics*. 2021;22:485-503.
15. Clayton AH, McGarvey EL, Abouesh AI. Substitution of an SSRI with bupropion sustained release following SSRI-induced sexual dysfunction. *Prim Care Companion J Clin Psychiatry*. 2001;3(2):89.
16. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. *J Clin Psychopharmacol*. 2009; 29(3):259-266.
17. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish working group for the study of psychotropic-related sexual dysfunction. *J Clin Psychiatry*. 2001;62 (Suppl 3):10-21.
18. O'Mullan C, Doherty M, Coates R, Tilley PJ. Women's experiences of coping with the sexual side effects of antidepressant medication. *Psychol Health*. 2014; 29:1388-1406.
19. Modell J, Katholi C, Modell J, De-Palma R. Comparative sexual side effects of bupropion, fuloxetine, paroxetine and sertraline. *Clin Pharmacol Ther.* 1997;61:476-487.
20. Clayton A, Keller A, McGarvey EL. Burden of phase-specific sexual dysfunction with SSRIs. *J Affect Disord.* 2006; *91*: 27–32.
21. Werneke U, Northey S, Bhugra D. Antidepressants and sexual dysfunction. *Acta Psychiatr Scand*. 2006;114(6): 384-397.
22. Thibaut F, Cosyns P, Fedoroff JP, Briken P, Goethals K, Bradford JMW. WFSBP task force on paraphilias. The world federation of societies of biological psychiatry (WFSBP) 2020 guidelines for the pharmacological treatment of paraphilic disorders. *World J Biol Psychiatry*. 2020;21:412-490.
23. McMahon CG, Abdo C, Incrocci L, et al. Disorders of orgasm and ejaculation in men. *J Sex Med*. 2004;1:58-65.
24. Atan A, Aslan Y. Premature ejaculation: the new definition and place of dapoxetine in current treatment. *Turkish J Urol.* 2010;36(2):149-154**.**
25. Incesu C. Sexual functions and sexual dysfunctions. *Clin Psychiatry.* 2004;3:3-13.
26. Althof SE, McMahon CG, Waldinger MD, et al. An update of the International Society of Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation (PE). *J Sex Med*. 2014;11(6):1392-1422.
27. DSM 5 diagnostic and statistical manual of mental disorder. American Psychiatry Association (APAA), 2013.
28. Waldinger MD. The neurobiological approach to premature ejaculation. *J Urol.* 2002;168:2359-2367.
29. Waldinger MD, Zwinderman AH, Olivier B. Antidepressants and ejaculation: a double-blind, randomized, placebo-controlled, fixed-dose study with paroxetine, sertraline, and nefazodone. *J Clin Psychopharmacol.* 2001;21(3): 293-297.
30. Giuliano F, Clément P. Serotonin and premature ejaculation: from physiology to patient management. *Eur Urol.* 2006;50(3):454-466.
31. Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. *Int J Impot Res*. 2004;16:369-381.
32. Waldinger MD, Berendsen HH, Blok BF, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. *Behav Brain Res*. 1998; 92:111-118.
33. Martin-Tuite P, Shindel AW. Management options for premature ejaculation and delayed ejaculation in men. *Sex Med Rev.* 2020;8:473-485.
34. Zhang D, Cheng Y, Wu K, Ma Q, Jiang J, Yan Z. Paroxetine in the treatment of premature ejaculation: a systematic review and meta-analysis. *BMC Urol*. 2019;3;19:22.
35. Arafa M, Shamloul R. A randomized study examining the effect of 3 SSRI on premature ejaculation using a validated questionnaire. *Ther Clin Risk Manag.* 2007;3:527-531.
36. McMahon CG, Jannini E, Waldinger M, Rowland D. Standard operating procedures in the disorders of orgasm and ejaculation. *J Sex Med*. 2013;10:204-229.
37. Russo A, Capogrosso P, Ventimiglia E, et al. Efficacy and safety of dapoxetine in treatment of premature ejaculation: an evidence-based review. *Int J Clin Pract*. 2016;70:723-733
38. Aversa A, Pili M, Francomano D, et al. Effects of vardenafil administration on intravaginal ejaculatory latency time in men with lifelong premature ejaculation. *Int J Impot Res*. 2009;21:221-227.
39. Kirby EW Tramadol for the management of premature ejaculation: a timely systematic review *Int J Import Res*. 2015; 27:121-127.
40. Hull EM, Muschamp JW, Sato S. Dopamine and serotonin: influences on male sexual behavior. *Physiol Behav.* 2004; 83:291-307.
41. de Jong TR, Veening JG, Olivier B, Waldinger MD. Oxytocin involvement in SSRI-induced delayed ejaculation: a review of animal studies. *J Sex Med*. 2007;4(1):14-28.
42. Nutt DJ, Forshall S, Bell C, et al. Mechanisms of action of selective serotonin reuptake inhibitors in the treatment of psychiatric disorders. *Eur Neuropsychopharmacol* 1999;9 (suppl 3):81-86.
43. Giuliano F, Clèment P. Pharmacology for the treatment of premature ejaculation. *Pharmacol Rev.* 2012;64:621-644.
44. Hillegaart V, Ahlenius S, Larsson K. Region-selective inhibition of male rat sexual behavior and motor performance by localized forebrain 5-HT injections: a comparison with effects produced by 8-OH-DPAT. *Behav Brain Res*. 1991;42:169-180.
45. Fernandez-Guasti A, Escalante AL, Ahlenius S, Hillegaart V, Larsson K. Stimulation of 5-HT1A and 5-HT1B receptors in brain regions and its effects on male rat sexual behaviour. *Eur J Pharmacol.* 1992;210:121-129.
46. Foreman MM, Hall JL, Love RL. The role of the 5-HT2 receptor in the regulation of sexual performance of male rats. *Life Sci.* 1989;45:1263-1270.
47. de Jong TR, Pattij T, Veening JG, et al. Citalopram combined with WAY 100635 inhibits ejaculation and ejacu- lation-related fos immunoreactivity. *Eur J Pharmacol.* 2005;509:49-59.
48. de Almeida Kiguti LR, Pacheco TL, Antunes E, Kempinas WG. Lorcaserin administration has pro-ejaculatory effects in rats via 5-HT_{2C} receptors activation: a putative pharmacologic strategy to delayed ejaculation? *J Sex Med.* 2020;17(6):1060-1071.
49. Looney C, Thor KB, Ricca D, Marson L. Differential effects of simultaneous or sequential administration of paroxetine and WAY-100,635 on ejaculatory behavior. *Pharmacol Biochem Behav.* 2005;82:427-433.

50. Yells DP, Prendergast MA, Hendricks SE, Nakamura M. Fluoxetine-induced inhibition of male rat copulatory behavior: modification by lesions of the nucleus paragigantocellularis. *Pharmacol Biochem Behav.* 1994;49:121-127.

51. Cantor JM, Binik YM, Pfaus JG. Chronic fluoxetine inhibits sexual behavior in the male rat: reversal with oxytocin. *Psychopharmacology (Berl).* 1999;144:355-362.

52. Renner U, Zeug A, Woehler A et al. Heterodimerization of serotonin receptors 5-HT1A and 5-HT7 differentially regulates receptor signalling and tracking. *J. Cell Sci. 2012;* 125, 2486-2499.

53. Naumenko VS, Popova NK, Lacivita E, Leopoldo M, Ponimaskin EG. Interplay between serotonin 5-HT1A and 5-HT7 receptors in depressive disorders. *CNS Neurosci Ther.* 2014:20:582-590.

54. Esquivel-Franco DC, Olivier B, Waldinger MD, Gutiérrez-Ospina G, Olivier JDA. Tramadol's inhibitory effects on sexual behavior: pharmacological studies in serotonin transporter knockout rats. *Front Pharmacol.* 2018;9:676.

55. Homberg JR, Olivier JDA, Smits BMG, et al. Characterization of the serotonin transporter knockout rat: a selective change in the functioning of the serotonergic system. *Neuroscience.* 2007;146:1662-1676.

56. Chan JSW, Snoeren EMS, Cuppen E, Waldinger MD, Olivier B, Oosting RS. The serotonin transporter plays an important role in male sexual behavior: a study in serotonin transporter knockout rats. *J Sex Med.* 2011;8:97-108.

57. Arias B, Catalán R, Gastó C, Gutiérrez B, Fañanás L. Evidence for a combined genetic effect of the 5-HT (1A) receptor and serotonin transporter genes in the clinical outcome of major depressive patients treated with citalopram. *J Psychopharmacol.* 2005;19:166-172.

58. Westenberg HGM, Sandner C. Tolerability and safety off fluvoxamine and other antidepressants. *Int J Clin Pract.* 2006;60(4):482-491.

59. Baldwin DS, Foong T. Antidepressant drugs and sexual dysfunction. *Br J Psychiatry.* 2013;202(6):396–397.

60. Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. *BMJ.* 1995;310:1433-1438.

61. Croft H, Settle E Jr, Houser T, Batey SR, Donahue RM, Ascher JA. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin Ther.* 1999;21:643-658.

62. Luft MJ, Dobson ET, Levine A, Croarkin PE, Strawn JR. Pharmacologic interventions for antidepressant-induced sexual dysfunction: a systematic review and network meta-analysis of trials using the Arizona sexual experience scale. *CNS Spectr.* 2021;12:1-10.

63. Montejo AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther.* 1997; 23:176-194.

64. Waldinger MD. Psychiatric disorders and sexual dysfunction. *Handb Clin Neurol.* 2015; 130:469-489.

65. Rothschild AJ. Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holidays. *Am J Psychiatry.* 1995;152:1514-1516.

66. Alipour-Kivi A, Eissazade N, Shariat SV, et al. The effect of drug holidays on sexual dysfunction in men treated with selective serotonin reuptake inhibitors (SSRIs) other than fluoxetine: an 8-week open-label randomized clinical trial. *BMC Psychiatry.* 2024;24:67.

67. Reichenpfader U, Gartlehner G, Morgan LC, et al. Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. *Drug Safety.* 2014;37:19–31.

68. Tripathi A, Agrawal A, Joshi M. Treatment-emergent sexual dysfunctions due to antidepressants: a primer on assessment and management strategies. *Indian J Psychiatry.* 2024; 66:293-303.

69. Gelenberg AJ, McGahuey C, Laukes C et al. Mirtazapine substitution in SSRI-induced sexual dysfunction. *J Clin Psychiatry.* 2000;61:356-360

70. Ferguson JM, Shrivastava RK, Stahl SM, et al. Reemergence of sexual dysfunction in patients with major depressive disorder: double-blind comparison of nefazodone and sertraline. *J Clin Psychiatry.* 2001;62:24-29.

71. Jacobsen PL, Mahableshwarkar AR, Chen Y, Chrones L, Clayton AH. Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well-treated major depressive disorder experiencing SSRI-induced sexual dysfunction. *J Sex Med.* 2015;12:2036-2048.

72. Montejo AL, Perez Urdaniz A, Mosqueira I, et al. EPA-1719 – effectiveness of switching to agomelatine in antidepressant-related sexual dysfunction. *Eur Psychiatry.* 2014;29:1.

73. Rizvi SJ, Kennedy SH. Management strategies for SSRI-induced sexual dysfunction. *J Psychiatry Neurosci.* 2013; 38:E27-28.

74. Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K. Strategies for managing sexual dysfunction induced by antidepressant medication. *Cochrane Database Syst Rev.* 2013:CD003382.

75. Walker PW, Cole JO, Gardner EA, et al. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. *J Clin Psychiatry.* 1993;54:459-465.

76. Kennedy SH, McCann SM, Masellis M, et al. Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. *J Clin Psychiatry.* 2002; 63:181-186.

77. Aizenberg D, Weizman A, Barak Y. Sildenafil for selective serotonin reuptake inhibitor-induced erectile dysfunction in elderly male depressed patients. *J Sex Marital Ther.* 2003;29:297–303.

78. Fava M, Nurnberg HG, Seidman SN, et al. Efficacy and safety of sildenafil in men with serotonergic antidepressant-associated erectile dysfunction: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry.* 2006;67:240-246.

79. Salerian AJ, Eric Deibler W, Vittone BJ, et al. Sildenafil for psychotropic-induced sexual dysfunction in 31 women and 61 men. *J Sex Marital Ther.* 2000;26:133-140.

80. Ozmenler NK, Karlidere T, Bozkurt A, et al. Mirtazapine augmentation in depressed patients with sexual dysfunction due to selective serotonin reuptake inhibitors. *Human Psychopharmacol.* 2008;23:321-326.

81. Landén M, Eriksson E, Agren H, Fahlén T. Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. *J Clin Psychopharmacol.* 1999;19:268-271.

82. Norden MJ. Buspirone treatment of sexual dysfunction associated with selective serotonin reuptake inhibitors. *Depression.* 1994;2:109-112.